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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	12

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/490,609	BUNCH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-24,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

PATRICIA [illegible]
PATENT ANALYST

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Claims 1-33 are pending in the instant application.

Election/Restriction

Claims 1-24, 29 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Applicant's election with traverse of Group IV, claims 25-28, with a species election of SEQ ID NOS: 280, 317, 337, 384, 465 and 488 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that all of the Groups relate to biomarkers of carcinogenesis and prior art searching of all of the compositions and methods in all of the Groups would not be undue burden to the examiner. This is not found persuasive because thorough searches required for all of the Groups, which Groups comprise patentably distinct compositions and methods, and furthermore comprise 580 distinct genes, would be burdensome to the examiner and the search required for a single gene would not constitute a thorough and coextensive search for the other 579 genes.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-28 and 31-33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "conditions permitting nucleic acid hybridization" in line 3 of claim 25 is unclear and needs to be clarified.

The phrase "substantially hybridizes" in lines 4 and 5 of claims 31 and 32 is unclear and needs to be clarified.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for observing the differences in the expression of various transcripts in liver cells obtained from rats following their exposure to phenobarbital, does not reasonably provide enablement for a method for determining a level or pattern of a carcinogenesis biomarker in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of determining a level or pattern of a carcinogenesis biomarker in any cell, or a method of determining the carcinogenicity of a composition,

comprising the hybridization of a marker nucleic acid molecule selected from SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488 with complementary nucleic acid molecules obtained from the cell, which cell has been exposed in vitro or in vivo to a potentially carcinogenic composition, and determining the absence or presence of mRNA which substantially hybridizes to at least one nucleic acid sequence selected from SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. Comparisons of expression patterns have been made by several laboratories between various neoplastic cells and untransformed cells, and some examples of these previous findings have been provided in the 102 rejections below. The changes in expression patterns between untransformed and neoplastic cells vary between cell types, and the examples provided in the instant specification are representative of liver cells upon exposure to phenobarbital, which are not generally applicable to the neoplastic transformation of all cell types following their exposure to any and/or all carcinogenic agents. Furthermore, a substance which is known to be carcinogenic to one cell type is not necessarily carcinogenic to all cell types and a carcinogenic agent which induces or suppresses the expression of a particular gene in one cell type does not necessarily produce the same phenotype in all cell types. In addition, a lack of correlation has been taught previously by Anderson et al between the expression of the most abundant liver mRNAs and the expression of the most abundant liver secreted proteins. These findings

illustrate the high level of unpredictability that exists in comparing mRNA abundances with protein abundances for a given cell type. (See especially the abstract, introduction and figure 3 on page 535 of Anderson et al).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of measuring the carcinogenicity of any and/or all potentially carcinogenic compositions in all cell types whereby differential expression of SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488 has been observed.

The specification teaches the relative abundance of a battery of mRNA's in rat liver cells following administration of phenobarbital in vivo, whereby differential mRNA expression is observed between untreated and treated liver cells using amplified fragment length polymorphism (AFLP) based transcript imaging technology, whereby restriction fragments are generated and tagged with specific adapters of known sequences, and which measured and differentially expressed mRNA's are those disclosed in figure 1. The specification fails to teach the differential expression of these biomarkers in any cell types other than liver cells following exposure to any carcinogenic agents other than phenobarbital, whereby carcinogenesis is detected for any composition in any and/or all cells. One skilled in the art would not accept on its face the examples given in the specification of the differential expression patterns of the various mRNA's shown in figure 1 following the exposure of liver cells to phenobarbital as being correlative or representative of the successful measurement of any and/or all carcinogens in any and/or all cell

types in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the detectability in all cell types of differential gene expression upon exposure to potential carcinogens. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with the tagging with specific adapters, amplification and successful detection of genes which are differentially expressed in all cell types following the administration of any carcinogenic composition.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to a method of determining a level or pattern of a carcinogenesis biomarker in any cell, or a method of determining the carcinogenicity of a composition, comprising the hybridization of a marker nucleic acid molecule selected from SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488 with complementary nucleic acid molecules obtained from the cell, which cell has been exposed in vitro or in vivo to a potentially carcinogenic composition, and determining the absence or presence of mRNA which substantially hybridizes to at least one nucleic acid sequence selected from SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488. The quantity of experimentation required to practice the invention claimed would require the *de novo* determination of the differential expression of SEQ ID NOS: 280, 317, 337, 337, 384, 465 and 488 upon the neoplastic transformation of all cell types upon exposure to any carcinogenic agent. Since determination of these factors for a particular biomarker in a particular cell type exposed to a particular carcinogen is highly

unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Hillman et al.

Hillman et al disclose the presence or absence of biomarker gene expression in the diagnosis of various cancers comprising measuring a difference in the expression pattern of SEQ ID NO: 317 (See especially columns 15-19 and the accompanying sequence alignments).

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Upton et al.

Upton et al disclose the differential expression of the biomarker mRNA of SEQ ID NO: 465 in leukemic cells (See entire document, especially the second paragraph of the introduction and the first paragraph of the experimental section on page 425; See the accompanying sequence alignments).

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al.

Lee et al disclose the differential expression of the biomarker mRNA of SEQ ID NO: 384 in various differentiated and undifferentiated cells, whereby a comparison of expression is correlated with the effects of drugs on gene expression and cancer progression (See entire

document, especially figure 1 on page 8305 and the last paragraph on page 8307; See accompanying sequence alignments).

Claims 25-27 and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Skoda et al.

Skoda et al disclose the differential expression of SEQ ID NO: 337 in various cancer cells, as well as disclosing the increased expression of nucleic acids encoding SEQ ID NO: 337 in response to exposure to carcinogenic intermediates (See entire document, especially the introduction on page 1549 and figure 5 on page 1553; See accompanying sequence alignments).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader,

can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER

JZ

August 9, 2001